Genome-wide association study and targeted metabolomics identifies sex-specific association of CPS1 with coronary artery disease.

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Public Summary:
Sought to identify genetic factors associated with plasma betaine levels and determine their effect on risk of coronary artery disease.

Scientific Abstract:
Metabolites derived from dietary choline and L-carnitine, such as trimethylamine N-oxide and betaine, have recently been identified as novel risk factors for atherosclerosis in mice and humans. We sought to identify genetic factors associated with plasma betaine levels and determine their effect on risk of coronary artery disease (CAD). A two-stage genome-wide association study (GWAS) identified two significantly associated loci on chromosomes 2q34 and 5q14.1. The lead variant on 2q24 (rs715) localizes to carbamoyl-phosphate synthase 1 (CPS1), which encodes a mitochondrial enzyme that catalyses the first committed reaction and rate-limiting step in the urea cycle. Rs715 is also significantly associated with decreased levels of urea cycle metabolites and increased plasma glycine levels. Notably, rs715 yield a strikingly significant and protective association with decreased risk of CAD in only women. These results suggest that glycine metabolism and/or the urea cycle represent potentially novel sex-specific mechanisms for the development of atherosclerosis.